AMENDMENTS TO THE SPECIFICATION:

Please insert before the first paragraph on page 1 the following:

The present application is a continuation-in-part of U.S. patent application 10/374,784 filed February 25, 2003, now pending, which claims benefit of provisional application 60/359,948, filed February 25, 2002, the entire disclosures of which are hereby incorporated by reference.

Please replace paragraph [0053] with the following:

As indicated above, the PTM molecules of the invention are also designed to contain a 3' splice region that may include a branchpoint, pyrimidine tract and a 3' splice acceptor AG site and/or a 5' splice donor site. Consensus sequences for the 5' splice donor site and the 3' splice region used in RNA splicing are well known in the art (*See*, Moore, *et al.*, 1993, The RNA World, Cold Spring Harbor Laboratory Press, p. 303-358). In addition, modified consensus sequences that maintain the ability to function as 5' donor splice sites and 3' splice regions may be used in the practice of the invention. Briefly, the 5' splice site consensus sequence is AG/GURAGU (SEQ ID NO. 1) (where A=adenosine, U=uracil, G=guanine, C=cytosine, R=purine and /=the splice site). The 3' splice site consists of three separate sequence elements: the branchpoint or branch site, a polypyrimidine tract and the 3' consensus sequence (YAG). The branchpoint consensus sequence in mammals is YNYURAC (SEQ ID NO. 2) (Y=pyrimidine). The underlined A is the site of branch formation. A polypyrimidine tract is located between the branchpoint and the splice site acceptor and is important for efficient branchpoint utilization and 3' splice site recognition.

Please replace paragraph [0099] with the following:

The binding domain of PTMs can be assembled from either PCR products or annealed oligonucleotides. The coding sequence for firefly luciferase is generated by PCR or directly cloning from commercially available plasmid cDNA (Promega). To reduce the possibility of self-expression of the PTM prior to *trans*-splicing, the initiator AUG codon

may be eliminated from the coding sequence during PCR amplification or cloning. As an example Luc-PTM1, shown in Figure 3, consists of an antisense target binding domain of 100-200 nt complementary to β-HCG6 intron 1, a spacer sequence, a yeast branchpoint consensus sequence (UACUAAC) (SEQ ID NO. 3), an extensive polypyrimidine tract (12-15 pyrimidines), a 3' acceptor site (AG dinucleotide) followed by the complete coding for firefly luciferase minus the initiator codon. One or more nucleotides may be added or removed to insert the coding sequence into the proper reading frame, so that upon *trans*-splicing, the luciferase gene will be in the translational frame with the remaining exons of the target pre-mRNA. Unique restriction sites are placed between each of the PTM elements, facilitating the replacement of individual elements. In addition, the binding domain may contain alternate sites that initiate transcription out of frame from the reporter gene thereby preventing translation and expression of unspliced PTMs.

Please replace paragraph [0104] with the following:

3' splice elements. 3' splice elements including the branchpoint (BP), the polypyrimidine tract (PPT) and a 3' acceptor site (AG dinucleotide) may also be included. *Trans*-splicing can be modulated by changing the sequence of the BP and the length and composition of the PPT. A yeast consensus branchpoint sequence UACUAAC (SEQ ID NO. 4) provides a greater rate of *trans*-splicing in mammalian cells (Puttaraju *et al.*, 1999 Nature Biotechnology 17:246-52).

Please replace paragraph [0106] with the following:

Untranslated regions. Modification of 3' UTR and RNA processing signals are also carried out to increase RNA processing and stability. To increase the stability of *trans*-spliced messages and ultimately the level of luciferase activity, alternative polyadenylation signals may be engineered in the 3' untranslated sequence. To maximize the efficiency of 3' end cleavage and polyadenylation of *trans*-spliced mRNA, each PTM construct can be modified by including GT rich sequences (consensus YGTGTTYY) (SEQ ID NO. 5) downstream of the poly-A signal. This consensus, initially identified in

herpes simplex virus genes, has been shown to be present in a large number of mammalian genes. Other modifications are also possible.

Please replace paragraph [0113] with the following:

To evaluate the potential use of spliceosome mediated RNA *trans*-splicing for expression of a light producing enzyme or protein, a luciferase model was developed. To quantify the level of luciferase generated by *trans*-splicing in cells and small animal models, a pre-mRNA target was constructed that expressed part of the synthetic Renilla or Firefly luciferase sequence, coupled to the coding sequences for HPV E7 and the sequence of HPV immediate upstream of E7 from the human papilloma virus (HPV) (Figure 6). The chimeric pre-mRNA target undergoes normal *cis*-splicing to produce an mRNA but no luciferase activity. A pre-*trans*-splicing molecule (PTM) was engineered that should base pair with the target intron and *trans*-splice the 3' luciferase 'exon', into the target producing full length luciferase mRNA capable of producing luciferase activity (Figure 7 and 8). This PTM (Luc-PTM13) contains an 80 bp targeting domain that is complementary to intron 1 of HPV mRNA, a branchpoint (UACUAAC) (SEQ ID NO. 6) and polypyrimidine tract, AG dinucleotide acceptor followed by 3' hemi luciferase 'exon'. This region was selected based on the results targeting this clinically relevant splice site in HPV mRNA, where as high as 70% *trans*-splicing efficiency was achieved in cell culture models. A splice mutant was also constructed by deleting both the branchpoint and polypyrimidine sequences. Using these constructs, accurate *trans*-splicing of luciferase PTM13 (Luc-PTM13) into HPV-LucT1 target in human cells was demonstrated. Human embryonic kidney cells were transfected with either target, PTM alone as controls or co-transfected with both target and PTM expression plasmids. In a separate transfection target and splice mutant PTM were co-transfected. RT-PCR analysis of total RNA using target and PTM specific primers produced the expected *trans*-spliced (435 bp) product only in cells that contained both target and PTM but not in controls (target, PTM alone and target + splice mutant PTM) (Figure 9).

Please replace paragraph [0120] with the following:

Total RNA (2.5 μg) from the transfections was converted to cDNA using the MMLV reverse transcriptase enzyme (Promega) in a 25 μl reaction following the manufacturers protocol with the addition of 50 units RNase Inhibitor (Invitrogen) and 200 ng Luc-11R PTM specific primer (5'AAGCTTTTACTGCTCGTTCTTCAGCACGC) (SEQ ID NO. 7). cDNA synthesis reactions were incubated at 42°C for 60 minutes followed by incubation at 95°C for 5 minutes. This cDNA template was used for PCR reactions. PCR amplifications were performed using 100 ng of primers and 1 μl template (RT reaction) per 50 μl PCR reaction. A typical reaction contained ~25 ng of cDNA template, 100 ng of primers: Luc-33R (5'-CAGGGTCGGACTCGATGAAC) (SEQ ID NO. 8) and, Luc-34F, 5'-GGATATCGCCCTGATCAAGAG) (SEQ ID NO. 9)
1 X REDTaq PCR buffer (10 mM Tris-HCl, pH 8.3, 50 mM KCl, 1.1 mM $MnCl_2$ and 0.1% gelatin), 200 μM dNTPs and 1.5 units of REDTaq DNA polymerase (Sigma, Saint Louis, Missouri). PCR reactions were performed with an initial pre-heating at 94°C for 2 minutes 30 seconds followed by 25-30 cycles of 94°C for 30 seconds (denaturation), 60°C for 36 seconds (annealing) and 72°C for 1 minute (extension) followed by a final extension at 72°C for 7 minutes. The PCR products were then analyzed on a 2% agarose gel and the DNA bands were visualized by staining with ethidium bromide.